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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,270	11/26/2003	James McSwiggen	02-326-A (400/046US)	4392

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,270	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ____. 20 DEC 2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 20 December 2004 was filed before the mailing date of the instant first action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and a signed and initialed copy is enclosed herewith.

Claim Objections

Claim 1 is objected to because of the following informalities: the phrase "to RNA sequence" appears to be missing an article. Amendment to recite "to a RNA sequence" would be corrective.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is drawn to the siRNA molecule of claim 1, wherein said siRNA molecule comprises at least one non-nucleotide. Compliance with the second paragraph of 35 USC 112 requires particularly pointing out and distinctly claiming the claimed subject matter. It is maintained that one of skill could not divine what the metes and bounds are of a non-nucleotide, since any "genus" would be defined by what it's not.

Claim 1, and by dependency claims 2, 3, and 16, recite the limitation "said first sequence" and "said second sequence" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The present application claims priority through multiple provisional and non-provisional applications, as well as international applications. However, the only application that discloses the instant invention in its totality is considered to be PCT/US02/16840, which is the first to disclose siRNA molecules which have a sequence complementary to an RNA sequence encoding HER2 or portion thereof, wherein each sequence of the siRNA comprise from about 19 to about 23 nucleotides and wherein at least one nucleotide is not a ribonucleotide. Accordingly the instant claims are accorded the filing date of the '840 application, which is 29 May 2002. Should applicants disagree, applicants are required to point out with specificity where all relevant limitations are taught in a single, earlier application.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (Nature May 2001, 411.494-498, applicants IDS).

The claims of the instant invention are drawn to siRNA molecules which have a sequence complementary to an RNA sequence encoding HER2 or portion thereof, wherein each sequence

of the siRNA comprise from about 19 to about 23 nucleotides and wherein at least one nucleotide is not a ribonucleotide. The invention also comprises such molecules comprising overhangs at either the 3'- or 5'- ends or both, or wherein said molecule is chemically synthesized or wherein one nucleotide is a 2'-deoxy nucleotide, or to such molecules in composition with pharmaceutically acceptable carriers or Diluents.

Elbashir et al. teaches siRNA molecules which have a sequence complementary to a portion of an RNA sequence encoding HER2. For example, siRNA duplex "uGL2" of Elbashir matches over nucleotides 14 through 19 to nucleotides 605 through 600 of the HER2 sequence of GenBank Accession Number X03363, wherein each sequence of the siRNA comprise from about 19 to about 23 nucleotides and wherein at least one nucleotide is not a ribonucleotide. Elbashir teaches that the molecule comprises overhangs at the 3'- ends, wherein said molecule is chemically synthesized, wherein at least one nucleotide is a 2'-deoxy nucleotide. Since the molecules of Elbashir are delivered in solution, such molecules are thus considered to be in composition with pharmaceutically acceptable carriers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir ("Elbashir I"; EMBO J. 20:6877-6888), in view of Elbashir et al.("Elbashir II"; Genes and Dev. 2001 15:188-200, applicants IDS), McSwiggen (WO 01/16312; applicant's IDS), and Froehler et al. (U. S. Patent Number 5,830,653).

The claims of the instant invention are drawn to siRNA molecules which have a sequence complementary to an RNA sequence encoding HER2 or portion thereof, wherein each sequence of the siRNA comprise from about 19 to about 23 nucleotides and wherein at least one nucleotide is not a ribonucleotide, wherein the siRNA molecule comprises an overhang at the 5' end and/or 3' end of the either strand. The invention is also drawn to such a siRNA that comprises 2'-deoxy 2'-fluoro nucleotides, or 2'-O-methyl, or 2'allyl nucleotides, or comprises phosphorothioate internucleotide linkages, or an abasic moiety, which may be at either end.

McSwiggen et al. teach ribozymes directed to an RNA encoding HER2. McSwiggen et al. also teach ribozymes that are modified to incorporate 2'-deoxy nucleotides or 2'-deoxy 2'-fluoro nucleotides, or 2'-O-methyl nucleotides, or a cap moiety at the 3' and/or 5'end, or wherein the cap moiety is an abasic or inverted deoxy abasic moiety, wherein all modifications are utilized for enhanced stability and bioavailability of the oligonucleotide ribozymes. McSwiggen is also considered to teach polynucleotide and non-polynucleotide linkers.

Elbashir I teaches methods of systematically testing the efficacy of modifying various positions within an siRNA with known tide modifications used for example in ribozyme an antisense technology, and teach that siRNA is a valuable tool for down regulating gene function.

Elbashir II et al. teaches that double stranded RNA oligos 21 and 22 nucleotides long and comprising modifications designed to prolong bioactivity are capable of mediating sequence specific downregulation of gene expression. Elbashir et al. further state that "siRNA duplexes may represent a new alternative to antisense or ribozyme therapeutics" (pg. 198).

Froehler et al. teach modifying oligonucleotides directed to the HER2 target to comprise 2'-allyl, 2'-methyl, 2'-deoxy, and 2'-fluoro modifications.

It would have been obvious to one of ordinary skill in the art to use the modified siRNA oligos of Elbashir I or II to target HER2 as taught by McSwiggen *et al.* It also would have been obvious to one of ordinary skill in the art to modify such double stranded oligos, as taught by Elbashir *et al.*, McSwiggen *et al.*, and Froehler *et al.*

One would have been motivated to make and use siRNA oligos targeted to HER2 because both McSwiggen and Froehler teach targeting HER2 in methods of investigating the role of HER2 in breast cancer using ribozymes and antisense oligonucleotide therapeutics that are closely related to the subject siRNA, and because Elbashir state that siRNA duplexes may represent a new alternative to antisense or ribozyme therapeutics. Furthermore, McSwiggen and Froehler *et al.* both teach modifying their respective oligonucleotides to incorporate 2'-deoxy nucleotides or 2'-deoxy 2'-fluoro nucleotides, or 2'-O-methyl nucleotides, or cap moieties at the 3' and/or 5'end, or abasic or or phosphorothioate linkages, all of which are used to evade endogenous nucleases, and/or increase binding affinity, and/or increase cellular penetration.

Finally, the use of such modifications in either of the sense or antisense strands of such RNA's would be found using routine optimization. By these express teachings of the prior art, one of ordinary skill would have been motivated to make siRNA oligos that target HER2, because Elbashir teaches that it is at least as useful as antisense and ribozymes, both of which were made and used by Froehler and McSwiggen respectively.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using such oligos because Froehler and McSwiggen teach making and using single and double stranded oligos, and teach the reagents, equipment and steps of chemical synthesis necessary to make such oligos, and further because Elbashir teach how to make such oligos and the assays necessary to verify their successful use. Accordingly, one of ordinary skill in the art would have considered the invention to be *prima facie* obvious at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. D. Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER